

38 <sup>37</sup> 54. A library according to claim ~~50~~, wherein the partially randomised zinc finger further has a random allocation of amino acids at position +8.

39 <sup>38</sup> 55. A library according to claim ~~54~~, wherein the zinc finger polypeptide is displayed on a viral particle.

310 40 <sup>38</sup> 56. A library according to claim ~~54~~, wherein the partially randomised zinc finger is positioned between two or more zinc fingers.

41 57. A library of DNA sequences, each sequence encoding a zinc finger polypeptide for display, the zinc finger polypeptide comprising at least one zinc finger having partially randomised allocation of amino acids, the partially randomised zinc finger having a random allocation of amino acids at positions -1, +2, +3, +6 and +8, position +1 being the first amino acid in the  $\alpha$ -helix of the zinc finger.--

REMARKS

Reconsideration and allowance are requested.

Claims 1-17, 19-22, 32-36 and 43-57 are pending.

Applicants acknowledge the courtesy of the Examiner in granting the interview conducted on March 13, 1998. It was

helpful to discuss the pending Office Action with Examiners Sandals and Deegan prior to preparation of this response.

The amendments to the specification and claims find support throughout the originally filed disclosure. In particular, the library may be displayed on substrates other than a viral particle (see, for example, stalled polysomes on page 11, last paragraph, of the specification) and the partially randomised zinc finger is not limited by position to being a middle finger (see page 5, first paragraph, of the specification). Moreover, the specification has been amended to include sequence identifiers. Thus, applicants submit that the amendments do not introduce new matter.

The Office Action alleges on page 2 that applicant is required to reference the foreign priority documents by amending the specification. The specification contains a reference to application PCT/GB95/01949. However, applicants submit that benefit of an earlier filing date does not require reference to foreign priority documents in the specification because priority has been claimed in the Declaration filed on June 2, 1997.

The specification has been amended to add generic terminology to accompany trademarks identified by the Examiner.

Substitute pages of the specification which contain the entire text are attached. The substitute pages are not

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believed to add new matter because the missing text appears to have been omitted prior to forwarding of the application by the International Bureau.

In accordance with the Examiner's requirement and 37 CFR 1.821 et seq., applicants submit a substitute paper copy and computer readable form (CRF) of the Sequence Listing. The Sequence Listing does not include new matter, and the contents of the paper copy and the CRF are the same. The sequences disclosed in the Figures, Table 1 and the text of the specification are listed in the Sequence Listing, and the specification includes sequence identifiers. Thus, applicants submit that the present application complies with the Sequence Rules and request that compliance be acknowledged by the Patent Office.

#### **CLAIM REJECTIONS - 35 U.S.C. 112**

Claims 18, 23-31 and 37-42 have been canceled without prejudice to prosecution of the claimed subject matter in another application. Although applicants traverse the rejections in numbered paragraphs 5 and 7-8 of the Office Action, the aforementioned claims were canceled to advance prosecution in this case and to obtain early allowance of the pending claims. Thus, the rejections of claims 23-30 and 37-42 are moot.

Claims 15-29 and 31 were rejected under Section 112, first paragraph, because the specification, while being enabled for DNA, does not allegedly provide enablement for any nucleic acid. Applicants traverse.

The Office Action cites Friesen et al. in support of the conclusion that undue experimentation would be required to obtain zinc finger polypeptides that bind nucleic acids other than DNA. However, the disclosure of Friesen et al. actually appears to teach that the criteria for DNA binding are likely to be similar to those for RNA binding.

The present application acknowledges that the use of randomisation at positions -1, +2, +3 and +6 is known from the prior art, because these positions are the positions at which the zinc finger contacts the DNA double helix. These are precisely the positions which are randomised by Friesen et al. in order to select an RNA-binding zinc finger polypeptide. This is set forth at page 10996, left column, under the heading "Phage Display of Zinc Fingers tz4-7".

Friesen et al. find these positions to be important for RNA binding, as noted in the discussion section of the cited reference. The paragraph bridging the left and right columns of page 10997 reads, "Our results suggest zinc finger recognition of RNA may be similar to DNA in that some contacts made by the  $\alpha$ -helix are identical to DNA contacts made by  $C_{2}H_{2}$  zinc fingers and DNA." This is reinforced in the abstract

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which states, "We propose that RNA binding by TFIID shows similarity to DNA binding in the use of the recognition sequence. Helix positions -1 and +2 may have particular significance for RNA binding."

Therefore, the teachings of Friesen et al. does not suggest that any different criteria should be applied to the selection of positions for randomisation in the design of an RNA-binding zinc finger polypeptide compared to the design of a DNA-binding zinc finger polypeptide. Accordingly, the conclusion which the Examiner draws from the cited reference is unwarranted.

Claims 4, 7-13, 16-17, 37-39 and 41 were rejected under Section 112, second paragraph, as allegedly indefinite. Applicants traverse because the claims have been amended to conform to U.S. practice and, thus, are submitted to be definite.

For all of the above reasons, applicants request that the rejections under Section 112 should be withdrawn.

#### **CLAIM REJECTIONS - 35 U.S.C. 103**

Claims 1-29 and 31-42 were rejected under Section 103 as being allegedly unpatentable over Jamieson et al. in view of Rebar et al., Thiesen et al., Jabobs, Nardelli et al., and Desjarlais et al. Applicants traverse.

On page 12 of the Office Action, the Examiner alleges that Jamieson et al. teaches a zinc finger "partially randomized at positions -1, +2, +3 and +6, and taught that the positions +1, +5 or ++8, were known to be randomized in a collection of naturally occurring zinc fingers". During the interview, the Examiner provided clarification that he was relying on statements made in the left column of page 5691 as teaching randomisation of positions +1 and +5; the Examiner acknowledged that Jamieson et al. did not teach randomising amino acid residues at position +8. As explained below, applicants submit that the statements made on page 5691 do not support a finding of prima facie obviousness.

The first statement relied upon by the Examiner is "The guanidinium groups of Arg side chains at positions 1 and 6 contact the 3' and 5' guanines, respectively (Figure 1)." Applicants submit that this alleged "teaching" is a printing error which would not suggest to one of ordinary skill in the art to randomise position +1.

The legend to Figure 1 of Jamieson et al. states, "The numbers -1, 2, 3, and 6 refer to positions on the zinc finger recognition helix that are involved in base contacts in the Zif268 cocrystal (Pavletich & Pabo, 1991). In finger 1, these correspond to Arg, Asp, Glu, and Arg, respectively." Furthermore, the three zinc fingers of Zif268 are aligned in Figure 2 of Jamieson et al. and that legend states, "Residues

18, 20, 21, and 24 correspond to helix positions -1, 2, 3, and 6 on finger 1 (Figure 1) and are marked with asterisks." Thus, the arginine residues in the zinc fingers of Zif268 are located at positions -1 and +6; a serine residue is located at position +1.

As was discussed with Examiner Sandals and Primary Examiner Degan at the interview on 13<sup>th</sup> March 1998, it is abundantly clear from the context of the cited reference that Jamieson et al. contains a printing error. Such error would neither teach nor suggest that position +1 contacted target DNA. There would accordingly have been no suggestion to one of ordinary skill in the art to randomise position +1.

The second statement relied upon by the Examiner is "In a separate library in which residues 3-5 were randomized, we found that Asp3 was selected exclusively." Such library does not anticipate the claimed invention because randomisation was not effected at positions -1, +2 and +6. Applicants submit that this statement would not suggest to one of ordinary skill in the art to randomise position +5 in a zinc finger because, while Jamieson et al. show a preference for certain residues at position +3, no significance was ascribed to the residue located at position +5. Therefore, the cited reference neither teaches nor suggests that one of ordinary skill in the art would have been motivated to randomise a zinc finger at position +5.

Applicants submit that one of ordinary skill in the art would not have been motivated on the basis of Jamieson et al. to randomise any one of positions +1, +5 and +8 in a zinc finger. Moreover, none of the secondary references cited by the Examiner cures this deficiency in Jamieson et al.

As stated in the Office Action, Rebar et al. randomised positions -1, +2, +3 and +6. They did not suggest randomising any one of positions +1, +5 and +8.

Thiesen et al. effected substitution of a zinc finger of SP1 into Kox 29 at finger 2 to substitute residues -1, +2, +3, +5 and +6. This was effected as a block substitution, and results in alteration of binding activity. However, the cited reference does not discuss randomising any one of the above identified positions. Moreover, Thiesen et al. provide no information regarding the individual effect of modifications at any one of positions -1, +2, +3, +5 and +6. In particular, the cited reference provides no information concerning the importance of position +5.

As stated in the Office Action, Jacobs et al. also fail to teach the randomisation of any one of positions +1, +5 and +8.

Nardelli et al. teach site-directed mutagenesis of zinc finger polypeptides in order to assess the importance of residues to binding activity. They do not teach randomisation



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of any particular residue, nor the importance of any one of positions +1, +5 and +8.

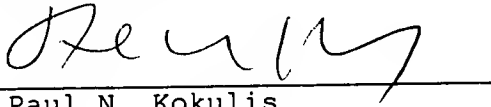
Desjarlais et al. teach methods for designing zinc finger polypeptides, not a method involving randomisation and selection.

In summary, it is submitted that a conclusion of nonobviousness must ensue because, even if it were considered obvious to combine the teachings of the cited references, no combination of those teachings actually suggests the claimed invention.

Having responded to all objections and rejections in the pending Office Action, applicants submit that the present claims are in condition for allowance and request an early Notice of same. The Examiner is invited to contact the undersigned if further information is needed.

Respectfully submitted,

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